REMARKS/ARGUMENTS

Rejection Under 35 USC 103(a)

In the Advisory Action dated June 15, 2005, the Examiner maintained his rejection of claims 1-7, 16, 21-26, 31-36, 38, 40, 42, 45, 48 and 52-57[1] under 35 USC 103(a) on the grounds that the claims are rendered obvious over Kissinger, et al. (Acta Crystallographica Section D, Biological Crrystallography, 1999, D44, 484-491).

1. Kissinger is not enabling as to multiple search models

Contrary to the Examiner's assertion, Applicants maintain that Kissinger is not enabling because the reference does not teach how to use multiple search models in Kissinger's evolutionary search procedure. Instead, Kissinger at most invites one to try to use Kissinger's evolutionary search procedure with multiple search models. Kissinger admits that only early (undisclosed) experiments were performed that suggest this approach is feasible. This is not an enabling teaching.

In support of the Examiner's maintenance of his rejection, the Examiner relies on the statement in Kissinger that "instead of a single search model, a set of structural models would be allowed to compete in the evolutionary search procedure [taught by Kissinger]." See Kissinger, page 490, Col 2, last paragraph. It is noted that Kissinger does not provide any teaching how multiple search models would "compete" using Kissinger's evolutionary search procedure.

2. The independent claims, as amended, specify non-iterative operation of the second computer executable logic relative to the first computer executable logic.

1 Examiner also rejects claim 49-51 but these claims are currently withdrawn.

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The independent claims have been amended to specify that the second computer executable logic operates in a **non-iterative** manner relative to the operation of the first computer executable logic. This claim language clearly distinguishes the independent claims from the evolutionary search procedure of Kissinger.

Kissinger and the present invention differ fundamentally with regard to the goal of each process. In Kissinger, the process uses an evolutionary search procedure to find the **best conditions** for performing a molecular replacement search using a given search model. In so doing, Kissinger **iteratively** optimizes the molecular replacement search conditions and the results that are produced. It is only at the end of Kissinger's iterative process that the **best conditions** for performing a molecular replacement search are identified. The end result in Kissinger is the identification of the **best conditions** for performing molecular replacement search using a given search model.

As noted above, Kissinger teaches that "a shortcoming of our method is that the search efficiency drops as the quality of the search model decreases." See Kissinger, page 490, Col 2, Second full paragraph. This shortcoming arises because Kissinger's process iterates to optimize the molecular replacement search parameters only for the selected search model.

By contrast to Kissinger, the present invention does not seek to find the best conditions for performing a molecular replacement search. Instead, the present invention operates to find the **best search model** to use without necessarily having optimized the conditions for performing molecular replacement.

The Examiner should note that the present invention does not exclude using an evolutionary molecular replacement search process. In fact, the Specification teaches using EMPR (See Specification, page 4, lines 5-6 and pages 27-34) as the first logic specified in the independent claims.

Unlike the Kissinger process which iterates until optimal conditions are found, the present invention only seeks to generate molecular replacement search results in order to have a basis for comparing search models. It is through the performance of the operations of the second computer executable logic that the **best search model** is identified.

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Once the best search model is identified with the aid of the second computer executable logic, Applicants are then free, for example, and as necessary, to go back and identify the best conditions for performing molecular replacement using the identified best search model.

3. Dependent claims further distinguish Kissinger

Claims 2-7 and 21-25

Applicants note dependent claims 2-7 and 21-25 specify the use of figures of merit to perform the comparisons being made by the second computer executable logic.

Kissinger provides no teaching or suggestion of this mode of operation for comparing search models. Furthermore, there is no need to use figures of merit in the Kissinger process because only the use of a single search model is explicitly taught by Kissinger. To the extent that the Examiner wishes to view Kissinger as being enabling for selecting a best search model, the Examiner should require the use of Kissinger's evolutionary search procedure for performing the selection since there is no teaching or suggestion by Kissinger that one may use other procedures to have multiple search models "compete."

In view of the failure of Kissinger to teach the use of figures of merit as a comparison method, Applicants submit that the Examiner's rejection of dependent claims 2-7 and 21-25 is unsupported and should be withdrawn on these further grounds.

Claims 16 and 38

The Examiner's attention is drawn to dependent claims 16 and 38 which in different ways claim the use of structurally dissimilar search models. Dependent claim 16 specifies that at least two different biomolecule structures (in the group) are structurally dissimilar to each other." Dependent claim 38 specifies "selecting at least two biomolecule structures

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that have less than 70% sequence identity with each other" which one of ordinary skill would expect would result in the selection of structurally dissimilar biomolecule structures.

By contrast to the present invention, Kissinger is dependent on using a search model that is structurally similar to the target protein. In regard to Kissinger's evolutionary search procedure, the reference specifically teaches that "a shortcoming of our method is that the search efficiency drops as the quality of the search model decreases." See Kissinger, page 490, Col 2, Second full paragraph. The reference also teaches at page 490, Col 2, last paragraph that having a set of structural models compete "will undoubtedly necessitate much larger population sizes and much longer computing times." Reading these two sentences in combination, one of ordinary skill would understand that if one were to try to use the teachings of Kissinger to have multiple search models compete, the multiple search models need to all be high quality search models.

In direct contrast to Kissinger, the present invention teaches that search models that are **POOR** structural matches to the target protein make the present invention work better. See Specification, page 14, line 25 – page 15, line 10 which teaches that

> By contrast, comparing molecular replacement solutions allows one to determine that a given search model is superior to the other search models tested. More specifically, given that very few search models will have significant structural identity with the biomolecule or biomolecule complex whose structure is being solved, comparison of molecular replacement solutions according to the present invention allows one to establish a background correlation level based on a statistically significant number of structures that do not match. This makes it possible to readily identify superior search models by looking for a significantly greater correlation than the background correlation level. By being able to evaluate how much superior a given search model is relative to other search models, one is also able to infer whether any of the search models have significant structural identity with the biomolecule or biomolecule complex whose structure is being solved. This thus allows one to select which search model to use as the search model for molecular replacement.

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As noted in the Specification at page 14, lines 27-29, "very few search models will have significant structural identity with the biomolecule or biomolecule complex whose structure is being solved." Rather than avoiding these search models as Kissinger suggests, these poor structural matches are used by the present invention to "establish a background correlation level" and enable superior search models to be readily identified "by looking for a significantly greater correlation than the background correlation level." In fact, as noted at in the Specification at page 15, line 2, it is best to have "a statistically significant number of structures that do not match."

In view of the teaching in Kissinger for the search model to be structurally similar to the target protein, Applicants submit that the Examiner's rejection of dependent claims 16 and 38 is unsupported and should be withdrawn on these further grounds.

Claims 26 and 31-34

Applicants note dependent claim 26 and the dependent claims depending therefrom which specify the use of computer executable logic to select biomolecule structures on which to perform the multiple molecular replacement searches. As noted above, Kissinger requires the search model(s) to be structurally similar to the target protein. By contrast, the present invention has no such limitation. Rather, the ability to process structurally dissimilar search models allows the software and processes of the present invention to use computer executable logic to select biomolecule structures on which to perform the multiple molecular replacement searches.

In view of Kissinger's failure to teach the computer executable logic specified in claim 26 and Kissinger's general incompatibility with such computer executable logic, the Examiner is further requested to withdraw the pending rejection as to dependent claim 26 and the claims depending therefrom.

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CONCLUSION

Applicants earnestly believe that they are entitled to a letters patent, and respectfully solicit the Examiner to expedite prosecution of this patent application to issuance. Should the Examiner have any questions, the Examiner is encouraged to telephone the undersigned.

Respectfully submitted,
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